

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Williams, et al.)	Group Art Unit 1652
)	
Appl. No.	:	Not yet assigned)	I hereby certify that this correspondence and all
)	marked attachments are being deposited with
Filed	:	Herewith)	the United States Postal Service as express mail
)	mail in an envelope addressed to Assistant
For	:	PEG-URATE OXIDASE)	Commissioner for Patents, Washington, D.C
		CONJUGATES AND USE)	20231, on
		THEREOF)	
)	
Examiner	:	Not yet assigned)	

April 19, 2001
(Date)

Sam K Tahmassebi, Reg No. 45,151

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to the examination on the merits of the captioned application, please enter the following amendments.

IN THE SPECIFICATION:

At page 1, line 2, please insert:

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RELATED APPLICATIONS

This application is a divisional of U.S. Patent Application Serial No. 09/370,084, entitled "PEG-URATE OXIDASE CONJUGATES AND USE THEREOF," filed August 6, 1999, by Williams, et al., which in turn claims priority to prior U.S. Patent Application Serial No. 09/130,392, entitled "PEG-URATE OXIDASE CONJUGATES AND USE THEREOF," filed August 6, 1998, by Williams, et al., and which was converted to provisional Application No. 60/219,318 on August 5, 1999, all of which are incorporated by reference herein in their entirety.--

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IN THE CLAIMS:

Please cancel all the pending claims 1-41.

Please add the following new claims 42-76:

42. (NEW) A method for isolating a tetrameric form of uricase from a solution of uricase, said solution comprising tetrameric uricase and uricase aggregates, comprising the steps of:

applying said solution to at least one separation column at a pH between about 9 and 10.5; and

recovering from said column one or more fractions that contain isolated tetrameric uricase, wherein said one or more fractions are substantially free of uricase aggregates.

43. (NEW) The method of Claim 42, wherein said solution of said uricase is applied to said column at a pH of 10.2.

44. (NEW) The method of Claim 42, wherein said separation is based on a property selected from the group consisting of ion exchange and size exclusion.

45. (NEW) The method of Claim 42, further comprising the step of analyzing said fractions to determine at least one property selected from the group consisting of the presence of said tetrameric uricase and the absence of uricase aggregates.

46. (NEW) The method of Claim 45, wherein said analyzing step comprises at least one analysis selected from the group consisting of chromatography, centrifugation, light scattering and electrophoresis.

47. (NEW) The method of Claim 46, wherein said chromatography is high performance liquid chromatography.

48. (NEW) The method of Claim 42, wherein said isolated tetrameric uricase contains less than about 10% uricase aggregates.

49. (NEW) An isolated tetrameric uricase produced by the method of Claim 42.

50. (NEW) The isolated tetrameric uricase of Claim 49, wherein the uricase is a mammalian uricase.

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51. (NEW) The isolated tetrameric uricase of Claim 50, wherein the uricase is porcine liver, bovine liver or ovine liver uricase.

52. (NEW) The isolated tetrameric uricase of Claim 49, wherein the uricase is recombinant.

53. (NEW) The isolated tetrameric uricase of Claim 52, wherein the uricase has substantially the sequence of porcine, bovine, ovine or baboon liver uricase.

54. (NEW) The isolated tetrameric uricase of Claim 52, wherein the uricase is chimeric.

55. (NEW) The isolated tetrameric uricase of Claim 54, wherein the chimeric uricase contains portions of porcine liver and baboon liver uricases.

56. (NEW) The isolated tetrameric uricase of Claim 55, wherein the chimeric uricase is pig-baboon chimeric uricase.

57. (NEW) The isolated tetrameric uricase of Claim 55, wherein the chimeric uricase is porcine uricase containing lysine in place of arginine at residue number 291 and serine in place of threonine at residue number 301.

58. (NEW) The isolated tetrameric uricase of Claim 52, wherein the uricase has substantially the sequence of baboon liver uricase in which tyrosine 97 has been replaced by histidine.

59. (NEW) The isolated tetrameric uricase of Claim 52, wherein the uricase comprises an amino terminal and a carboxyl terminal, and wherein the uricase is truncated at one terminal or both terminals.

60. (NEW) The isolated tetrameric uricase of Claim 49, wherein the uricase is a fungal or microbial uricase.

61. (NEW) The isolated tetrameric uricase of Claim 60, wherein the fungal or microbial uricase is isolated from *Aspergillus flavus*, *Arthrobacter globiformis*, *Bacillus sp.*, or *Candida utilis*, or is a recombinant enzyme having substantially the sequence of one of those uricases.

62. (NEW) The isolated tetrameric uricase of Claim 49, wherein the uricase is an invertebrate uricase.

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63. (NEW) The isolated tetrameric uricase of Claim 62, wherein the invertebrate uricase is isolated from *Drosophila melanogaster* or *Drosophila pseudoobscura*, or is a recombinant enzyme having substantially the sequence of one of those uricases.

64. (NEW) The isolated tetrameric uricase of Claim 49, wherein the uricase is a plant uricase.

65. (NEW) The isolated tetrameric uricase of Claim 64, wherein the plant uricase is isolated from root nodules of *Glycine max* or is a recombinant enzyme having substantially the sequence of that uricase.

66. (NEW) The isolated tetrameric uricase of Claim 49, each subunit of the uricase being subsequently covalently linked to an average of 2 to 10 strands of PEG to form a PEG-uricase conjugate, wherein each molecule of PEG has a molecular weight between about 5 kDa and 100 kDa, and wherein the conjugate retains at least about 75% of the uricolytic activity of unconjugated uricase and is substantially non-immunogenic.

67. (NEW) The isolated tetrameric uricase of Claim 66, wherein the PEG has an average molecular weight between about 10 kDa and 60 kDa.

68. (NEW) The isolated tetrameric uricase of Claim 67, wherein the PEG has an average molecular weight between about 20 kDa and 40 kDa.

69. (NEW) The isolated tetrameric uricase of Claim 66, wherein the average number of covalently coupled strands of PEG is 3 to 8 strands per uricase subunit.

70. (NEW) The isolated tetrameric uricase of Claim 69, wherein the average number of covalently coupled strands of PEG is 4 to 6 strands per uricase subunit.

71. (NEW) The isolated tetrameric uricase of Claim 66, wherein the strands of PEG are covalently coupled to uricase via linkages selected from the group consisting of urethane linkages, secondary amine linkages, and amide linkages.

72. (NEW) The isolated tetrameric uricase of Claim 66, wherein the PEG is linear.

73. (NEW) The isolated tetrameric uricase of Claim 66, wherein the PEG is branched.

74. (NEW) A pharmaceutical composition for lowering uric acid levels in a body fluid or tissue, comprising the isolated tetrameric uricase of Claim 49 and a pharmaceutically acceptable carrier.

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75. (NEW) The pharmaceutical composition of Claim 74, wherein said composition is stabilized by lyophilization and dissolves promptly upon reconstitution to provide solutions suitable for parenteral administration.

76. (NEW) The pharmaceutical composition of Claim 74, wherein said composition is stabilized by lyophilization and dissolves promptly upon reconstitution to provide solutions suitable for administration through inhalation.

REMARKS

By present amendments, Applicants have incorporated into the specification a paragraph indicating that the present application is a divisional of a pending U.S. application, to which the present application claims priority. Applicants have also included a new set of claims to be examined with this application. The new claims are drawn to the subject matter of the Group III claims, as set forth in the Restriction Requirement of March 21, 2001 in the parent case. Applicants maintain that the new claims add no new matter and are fully supported by the specification. By these amendments, Applicants make no admission as to the patentability of the original claims and the amendments should not be so construed.

Applicants maintain that the claims as presented herewith are allowable. A notice to that effect is respectfully requested.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: April 19, 2001

By: Sam K. Tahmassebi

Sam K. Tahmassebi
Registration No. 45,151
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660

AMEND

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